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Attorney Docket No. 9310.22CX

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Goudsmit et al.
Application Serial No: 09/463,352 Group Art Unit: 1655
Filed: January 21, 2000 Examiner: B. Sisson
For: *NUCLEIC ACID SEQUENCES THAT CAN BE USED AS PRIMERS AND PROBES IN THE AMPLICATION AND DETECTION OF ALL SUBTYPES OF HIV-1*

MAIL STOP RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

**DECLARATION OF JAAP GOUDSMIT, PIETER OUDSHOORN, SUZANNE JURRIAANS AND VLADIMIR VLADIMIROVICH LUKASHOV UNDER 37 C.F.R. § 1.131**

Sir:

We, Jaap Goudsmit, Pieter Oudshoorn, Suzanne Jurriaans and Vladimir Vladimirovich Lukashov hereby declare that:

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2. Prior to June 25, 1997, we conceived and reduced to practice the oligonucleotides having the nucleotide sequence of SEQ ID NOs 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 and 11, respectively, as recited in the pending claims, as well as methods of use and kits employing these oligonucleotides to detect HIV-1 nucleic acid in a sample

3. In support of the above statement, we hereby submit as Appendix A a copy of relevant pages of an internal memorandum entitled "Feasability of a qualitative NASBA assay with a broad HIV-1 clade reactivity" prepared by non-inventor, F. Jacobs, under the direction of

group leader and inventor, Pieter Oudshoorn, and submitted to Akzo Nobel. The dates within this document have been blocked out, but are before June 25, 1997.

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|---|---|
| Jaap Goudsmit | Date |
| Pieter Oudshoorn | Oct 1st 2003<br>Date |
| Suzanne Jurriaans | Date |
| Vladimir Vladimirovich Lukashov | Date |

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| Pieter Oudshoorn | Date |
| Suzanne Jurriaans | 30 Oct 2003<br>Date |
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| Suzanne Jurriaans | Date |
| Vladimir Vladimirovich Lukashov | Oktober 6, 2003<br>Date |

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Jaap Goudsmit — October 3, 2003
Date

Pieter Oudshoorn — Date

Suzanne Jurriaans — Date

Vladimir Vladimirovich Lukashov — Date

AKZO NOBEL

Pharma Group
Organon Teknika bv
Boxtel The Netherlands

Confidential
R&D
Diagnostics

SUBJMEMO
8747.970379

KOPIE

Identification:

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| DMS nr: | 8747.970379 | Doc. Type: | REPORT | Proj. nr.: | 423020 |
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| Title: | **Feasibility of a qualitative NASBA assay with a broad HIV-1 clade reactivity.** | | | | |
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| Date created: | | | | | |
| Relevant DMRs: | | | | | |
| Keywords: | | | | | |

| Author: | Name: | Date: | Signature |
|---|---|---|---|
| Department: | | | |
| NDU | F. Jacobs | | |

| Approval: | Name: | Date: | Signature |
|---|---|---|---|
| Function: | | | |
| Groupleader | P. Oudshoorn | | |

**To be returned to R&D secretary before submitting for final approval**

| Final authorization: | Name: | Date: | Signature |
|---|---|---|---|
| Function: | | | |
| NDU manager | C. v. Buul | | |

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## 2. Materials and methods

### 2.1 Design of primers and probes.

. The oligonucleotide sequences are respectively:

P1.1: *aat tct aat acg act cac tat agg gAG AGG* GGC GCC ACT GCT AGA GA
P1.2: *aat tct aat acg act cac tat agg gAG AGG* TTC GGG CGC CAC TGC TAG A
U5 end: *aat tct aat acg act cac tat agg g*CGGGCGCCACTGCTA
P2.1: CTG CTT AAA GCC TCA ATA AA
P2.2: CTC AAT AAA GCT TGC CTT GA

To perform ECL detection one biotin probe and two different detection probes were designed with the following sequences:

HIV-1 LTR-bio: TCT GGT AAC TAG AGA TCC CTC
HIV-LTR-AMN1: TAG TGT GTG CCC GTC TGT.
HIV-LTR-AMN2: AGT GTG TGC CCG TCT GTT.

## 2.2 Evaluation and optimization of the primers and probes.

The primers were tested directly in the amplification in the combinations P1.1/P2.1, P1.1/P2.2, P1.2/P2.1, P1.2/P2.2 and U5-end/P2.2 on in vitro *LTR* RNA and on Scott Layne RNA (subtype B, stock solution of $5.5*10^9$ copies RNA/ml). The input of the RNA was $10^4$ copies. The amplifications were examined on a 2% agarose gel and then blotted in 1 hour on zeta probe and cross-linked with UV. The blot was hybridized with the biotin probe (3 µM) by incubating the blot for 4 hours at 50°C. After hybridization the blot was washed two times for 5 minutes with 3*SSC/1%SDS solution at 50°C and one time for 10 minutes with 2*SSPE/0.1%SDS solution at RT. After this the blot was incubated for 30 minutes with 2 µl streptavidine/HRP solution (500 U/ml, Enhanced ChemiLuminiscense detection kit from Amersham) in 10 ml 5*SSPE/0.5%SDS. The blot was again washed two times for 5 minutes in 2*SSPE/0.1%SDS solution and one time for 10 minutes in 2*SSPE solution. The blot was dried between tissues and developed with the development solutions from the enhanced chemiluminiscense kit (Amersham). The blot was wrapped in Saran wrap and a film was placed on the blot for a couple of seconds. The film was developed according to the standard procedures.

## 3.2 Evaluation of selected primers.

*Figure 3. Detection of the amplimers on blot.*
*The primersets used were: nr 1: P1.1-P2.1, nr 2: P1.1-P2.2, nr 3: P1.2-P2.1, nr 4: P1.2-P2.2, nr 5: U5 end-5'LTRSph1. The RNA used as input were: A: in vitro RNA $10^4$ copies per input, B: Scott Layne RNA $10^4$ copies per input, C: No Templates.*